REMARKS

Claim 1 has been amended. Support for the amendment can be found in the Specification as filed, on page 4, lines 16-17 and the original Claim 12. Claim 12 has been canceled as redundant. No new matter has been introduced by this amendment. The following addresses the substance of the Office Action.

Non-obviousness

The Examiner has continued rejecting Claims 1-4 and 6-14 under 35 USC §103(a) as being allegedly obvious over USP 6,703,017 or USP 5,425,764, or USP 5,629,194 each in view of Posselt et al. (Diabetes, 1992, 41:771-775).

> Pursuant to MPEP 2143, in order to establish a *prima facie* case of obviousness three requirements must be met: First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> Furthermore, "Obviousness analysis requires <...> to assess invention as a whole to determine whether there was suggestion or motivation to combine prior art references, without engaging in improper "hindsight" determination <...>. <...> motivation to combine may be found in nature of problem to be solved, leading inventors to look to references relating to possible solutions to that problem" *Ruiz v. A.B. Chance Co.* 69 USPQ2d 1686-1691.

In the case of the present invention, the cited references fail to suggest all of the claim limitations, and in fact actually teach away from the presently claimed invention. As discussed in the previous response to Office Action, and as acknowledged by the Examiner, USP '017 or USP'764 or USP'194 do not teach a method for treating diabetes in a mammal comprising administration of two doses of insulin-secreting cells: one – tolerizing and one – therapeutic, wherein the tolerizing dose is at least one order of magnitude less that the therapeutic dose. The problem of rejection of the implants of the USP '017 or USP'764 or USP'194 is addressed differently: by reduction of antigenicity or by encapsulation of islet-producing stem cells in USP'017, by encapsulation of islets of Langerhans in USP'764, and by altering antigens on the cell surface of the porcine pancreatic cells or by using immunosuppressant drugs in USP'194. If a skilled artisan was still looking for other ways to solve the same problem of creating tolerance

to the implant, the publication of Posselt would point the artisan only in one direction: intrathymic implantation of a tolerizing dose of insulin-producing cells.

Posselt et al. describes implanting unencapsulated islets into various areas of the body, liver, kidney, and thymus, but the only implantation site that showed survival of the implanted cells was the thymus. As the authors stated several times in this article, thymus is considered to be an immunologically privileged site and is subject to the usual biologic characteristics of such sites, in that prior sensitization of the host with skin allografts precludes prolonged survival of intrathymic islets (page 272, right column). The experiments, performed by Posselt et al. show just that, i.e. when allogeneic islets were transplanted into the thymus of recipients that had previously rejected donor strain skin grafts, the islets were destroyed in an accelerated manner, demonstrating that the intrathymic site is readily accessible to activated T cells (page 367 left column, and page 368, right column), and that no tolerance can be achieved using this protocol. Furthermore, Posselt et al. goes on stating that the achieved tolerization to intrathymic allografts is due to their direct influence on maturing thymocytes, which are more susceptible to tolerance-inducing signals, and that such "inappropriate" presentation of antigen by nonlymphoid cells induce a state of anergy in T cells (page 373). Therefore, Posselt et al. actually teaches away from using the tolerizing dose of insulin-producing cells anywhere but thymus, and it only shows success in the absence of prior sensitization to the implant. As such, one skilled in the art would have no reasonable expectation of success in using the invention of the presently recited claims involving subcapsular, subcutaneous, intraperitoneal or intraportal implantation, and would have no motivation to do so.

The Applicant was the first one to teach that implantation of insulin-producing cells in sites other than thymus produces tolerance to the implanted cells. The Declaration of Dr. Scharp, submitted on May 6, 2005, reiterates that. The instant method as claimed in the presently amended Claim 1 specifies the non-thymus implantation sites for the tolerizing dose of encapsulated cells. This limitation is not suggested in any of the cited references.

Therefore, the cited references combined fail to provide a reasonable expectation of success or suggest all of the claim limitations. As such, the cited references fail to support a *prima facie* case of obviousness. Therefore, Claims 1-4 and 6-14 are in compliance with 35 U.S.C. 103.

The Examiner has continued rejecting Claim 5 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194 each in view Posselt et al. (1991 *Ann. Surg.* **214**:363-373) as applied to Claims 1-4 and 6-14, and further in view of USP 5,529,914. Non-obviousness of the independent Claim 1 in view of US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194 each in view Posselt et al. is asserted above. The US Patent 5,529,914 discloses a method of encapsulating cells, but it fails to cure the deficiencies of US Patent 6,703,017, US Patent 5,425,764, US Patent 5,629,194, and Posselt et al. Therefore, Claim 5 is in compliance with 35 USC §103(a).

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 17, 2005

By: _____

Marina L. Gordey
Registration No. 52,950
Agent of Record
Customer No. 20,995
(805) 547-5580

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